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Adverse Effect of Rifampin on Quinine Efficacy in Uncomplicated Falciparum Malaria

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The effects of adding rifampin to quinine were assessed in adults with uncomplicated falciparum malaria. Patients were randomized to receive oral quinine either alone ($n = 30$) or in combination with rifampin ($n = 29$). Although parasite clearance times were shorter in the quinine-rifampin-treated patients (mean ± standard deviation, 70 ± 21 versus 82 ± 18 h; $P = 0.023$), recrudescence rates were five times higher ($n = 15$ of 23; 65%) than those obtained with quinine alone ($n = 3$ of 25; 12%), $P < 0.001$. Patients receiving rifampin had significantly greater conversion of quinine to 3-hydroxyquinine and consequently considerably lower concentrations of quinine in their plasma after the second day of treatment (median area under the plasma drug concentration-time curve from day zero to day 7 = 11.7 versus 47.5 μg/ml · day, $P < 0.001$). Rifampin significantly increases the metabolic clearance of quinine and thereby reduces cure rates. Rifampin should not be combined with quinine for the treatment of malaria, and the doses of quinine should probably be increased in patients who are already receiving rifampin treatment.

Multidrug-resistant *Plasmodium falciparum* is an important public health problem in many areas where malaria is endemic. The efficacy of the major antimalarial drugs has declined in recent years, and the choice of effective antimalarial drugs is increasingly limited. This is a particular problem in Southeast Asia, where *P. falciparum* has developed resistance to chloroquine, pyrimethamine-sulfadoxine, and more recently mefloquine (10, 21). The use of antimalarial drugs in combinations usually improves cure rates and also prevents or delays the emergence of antimalarial drug resistance. The combination used is usually an antimalarial-antibiotic combination or two structurally unrelated antimalarials. For adult patients, combination treatments with quinine (Q)-tetracycline, Q-clindamycin, artesunate-mefloquine, and artemether-lumefantrine are effective worldwide, providing >90% cure rates. Q plus tetracycline or doxycycline is a generally safe and effective regimen, but it cannot be used in children less than 8 years old or during pregnancy. Q-clindamycin has proved an effective and well-tolerated alternative in adults and children with acute malaria (5, 11, 17), but clindamycin is significantly more expensive than tetracycline.

The antibiotic rifampin has been shown to have antimalarial activity in experimental studies (1, 16) and in patients with vivax malaria (12). Rifampin is a major component of first-line antituberculosis chemotherapy regimens. It is generally available and inexpensive and can be given to children and pregnant women. It was therefore a potential alternative antibiotic for combination with Q in the treatment of malaria. However, rifampin is a general potent inducer of hepatic microsomal enzyme activity that augments drug metabolism. The present study evaluated the effects of rifampin on both the efficacy and pharmacokinetics of Q in adult patients with uncomplicated falciparum malaria.

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MATERIALS AND METHODS

Patients. This study was conducted with adult male patients with acute *P. falciparum* malaria admitted to the Bangkok Hospital for Tropical Diseases, Bangkok, Thailand. Informed consent was obtained from each patient. Excluded from the study were patients with severe malaria (22) or patients with mixed malaria infections. Patients who gave a history of chronic cigarette smoking or drug hypersensitivity, who had taken any antimalarial drugs within the previous 48 h, or whose urine was positive in screening tests for sulfonamides (lignin test) or 4-aminoquinolines (Wilson-Edeson test) were also excluded. The study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Management. After clinical assessment and confirmation of the diagnosis from thick and thin blood smears, baseline blood samples were taken for routine hematologic and biochemical analyses. Patients were then allocated in accordance with the randomization chart to a 7-day regimen of oral treatment with Q sulfate (10 mg of salt/kg three times a day; Thai Government Pharmaceutical Organization) either alone or in combination with rifampin (R) (15 mg/kg/day for 7 days; Merrell Dow Pharmaceuticals Inc.). Oral acetaminophen (0.5 to 1 g every 4 h) was given for fevers of >38°C. Vital signs were recorded every 4 h until fever resolution and thereafter every 6 to 12 h. Fever clearance times were expressed as FCT_A, the time required for the body temperature to fall below 37.5°C, and FCT_B, the time required for the body temperature to fall below 37.5°C and remain below this value for >48 h. Patients who were unable subsequently to stay in the hospital until clearance of both fever and parasites were excluded from the study. Reappearance of infection was assessed in patients who remained in Bangkok either in the hospital or at home (i.e., outside the malaria transmission area) for at least 28 days. Patients with recrudescence were retreated with a 7-day course of Q (10 mg of salt/kg three times a day) combined with tetracycline (4 mg/kg four times a day; Thai Government Pharmaceutical Organization), and those who had late vivax appearances were treated subsequently with the standard doses of chloroquine and primaquine.

Laboratory investigations. Parasite counts were measured every 12 h in Giemsa-stained thin films or thick films until clearance and daily thereafter for 28

TABLE 1. Laboratory findings on admission in patients with *P. falciparum* malaria[a]

Parameter	Q	QR	Both groups	*P* value
No. of patients	30	29	59	
Age (yr)	24.1 ± 9.7	24.4 ± 7.7	24.2 ± 8.7	0.90
Wt (kg)	50.2 ± 8.4	51.0 ± 6.4	50.6 ± 7.4	0.69
No. (%) of patients with previous malaria	17 (57)	13 (45)	30 (51)	0.34
No. (%) coming from the West	26 (87)	22 (76)	48 (81)	0.33
No. of parasites/μl	9,394	19,690	13,513	0.14
Hematocrit (%)	33.7 ± 8.6	32.7 ± 8.1	33.3 ± 8.3	0.62
WBC[b] count (10^3/μl)	6.3 ± 1.9	6.5 ± 2.2	6.4 ± 2.0	0.74
Platelet count (10^9/liter)	102 ± 64	101 ± 69	101 ± 65	0.95
Serum creatinine (mg/dl)	1.02 ± 0.26	1.21 ± 0.38	1.1 ± 0.33	0.39
Total bilirubin (mg/dl)	1.4 (0.3–10)	1.4 (0.5–13.0)	1.4 (0.3–13)	0.71
SGPT[c] (U/liter)	30 (10–270)	32 (10–147)	30 (10–270)	0.65

[a] Data are shown as the mean ± SD, median (range), or geometric mean number.
[b] WBC, white blood cell.
[c] SGPT, serum glutamic pyruvic transaminase.

days. Parasite density was expressed as the number of parasites per microliter of blood. This was derived from the hematocrit and the numbers of parasites per 1,000 red blood cells in a thin film stained with Giemsa or Field stain or calculated from the white cell count and the number of parasites per 200 white blood cells in a thick film. The following variables were chosen prospectively to describe parasite clearance: times elapsed from the start of antimalarial treatment until the asexual-parasite count fell to 50 and 90% of the admission value and the time required to clear the asexual parasites in a peripheral blood smear (PCT). Routine biochemical and hematological tests were repeated on days 7, 14, 21, and 28 after admission.

Q pharmacokinetics. Serial venous blood samples were taken for determination of Q levels before and during treatment at 12 and 24 h and then daily until day 7. All blood samples were taken before Q intake. Each sample (4 ml) was collected in a heparinized tube and centrifuged immediately at 1,500 × g for 10 min. All plasma samples were stored at −20°C until analysis. Q and 3-hydroxy-Q (3-OH-Q) concentrations in plasma were assayed by high-performance liquid chromatography as described previously (18, 24). All drug measurements were carried out without knowledge of the treatment regimens given to the patients.

Q pharmacokinetics were evaluated by noncompartmental modeling with the Win-NONLIN program (Statistical Consultants, Lexington, Ky.). The areas under the plasma drug concentration-time curves from day zero to day 7 ($AUC_{0\text{-}7}$s) were calculated. The AUCs of Q and 3-OH-Q were calculated during the acute phase of illness (days 0 to 2 of the therapeutic course) and during recovery (days 2 to 7 of the therapeutic course) as $AUC_{0\text{-}2}$ and $AUC_{3\text{-}7}$, respectively. The maximum concentration of the drug in plasma (C_{max}) and the time to achievement of the C_{max} were calculated from the 7-day sequential Q and 3-OH-Q concentrations.

Statistical analysis. Normally distributed data were compared by unpaired *t* tests, and data not conforming to a normal distribution were compared by using the Mann-Whitney U test. The cumulative cure rate was calculated by Kaplan-Meier survival analysis and compared by using the Logrank test. Correlations were assessed by the method of Spearman. All statistical analyses were performed by the statistical computing package SPSS Version 10.0 for Windows (SSPS Inc.).

RESULTS

Patients. The study included 59 male patients with *P. falciparum* malaria. The mean (standard deviation [SD]) age was 24.2 (8.7) years. The majority of the patients (n = 48; 81%) came from the western border of Thailand, where *P. falciparum* is resistant to chloroquine, sulfadoxine-pyrimethamine, and mefloquine. Only half of the patients (n = 30; 51%) had a history of previous malaria infection. The mean (SD) number of previous malaria infections was 2.1(1.4), and the range was 1 to 6. The study patients were randomized to a 7-day course of either Q (n = 30) or QR (n = 29). Between the two treatment groups, there were no significant differences in age, body weight, geographic origin, parasite count on admission, or incidence of previous malaria attacks ($P > 0.09$) (Table 1). The baseline laboratory data were also not significantly different between the two groups. None of the patients in either group had elevated serum creatinine (i.e., serum creatinine was <3 mg/dl). Elevated serum bilirubin concentrations (total bilirubin, ≥3 mg/dl) were noted in 11 patients (Q, n = 6; QR, n = 5). None of the patients with hyperbilirubinemia had any other complications, and none had a parasite count of $>10^5$/μl.

Clinical responses. All of the patients recovered following treatment, and none had any serious adverse effects. The median FCT_A was 8 h, the median FCT_B was 51 h, and there were no significant differences in the patterns of fever clearance between patients treated with Q and those treated with QR ($P > 0.54$). The overall mean (SD) parasite clearance time was 76.2 (20) h, and the range was 21 to 126 h. Patients treated with QR had significantly shorter PCTs than did patients treated with Q (70.1 ± 20.8 versus 82.1 ± 17.6 h; P = 0.023). There were no significant differences in other measurements of parasite clearance between the two groups (time elapsed from the start of antimalarial treatment until the asexual parasite count fell to 50% = 19.8 ± 13.9 versus 15.4 ± 9.9 h; time elapsed from the start of antimalarial treatment until the asexual parasite count fell to 90% = 58.7 ± 19.5 versus 52.0 ± 17.2 h, respectively; $P > 0.12$). Patients admitted with hyperbilirubinemia (total serum bilirubin, ≥3 mg/dl) had significantly longer fever clearance times (median FCT_B [range] = 88 [8 to 176] h) than the remaining patients (38 [4 to 129] h) (P = 0.003), but the PCTs were not significantly different between the patients with jaundice and those without jaundice (mean ± SD = 86.6 ± 24.8 versus 74.2 ± 18.3 h; P = 0.07). After stratification for jaundice, the PCT remained significantly shorter in patients treated with QR than in those treated with Q alone. The PCTs of all of the study patients correlated positively with the FCT_B (r = 0.44, P = 0.001). There was also a significant correlation between total bilirubin on admission and FCT_B (r = 0.45, P = 0.001) but not between total bilirubin on admission and PCT (r = 0.14, P = 0.30).

Clinical course. Following treatment, 48 (81%) patients could either be followed up for at least 28 days outside the malaria transmission area or remained in the hospital until the

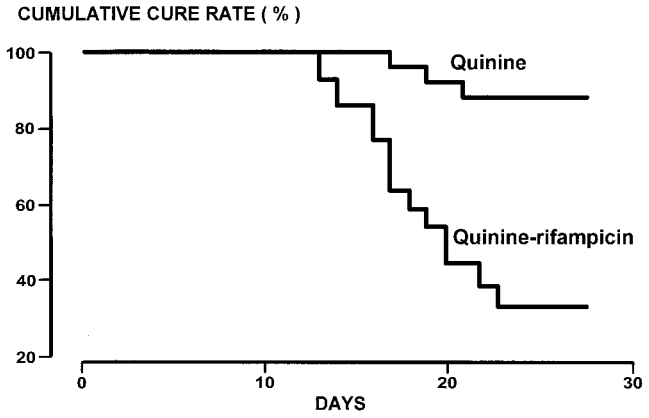

FIG. 1. Cumulative cure rates of patients with *P. falciparum* malaria randomized to treatment with either Q alone or QR.

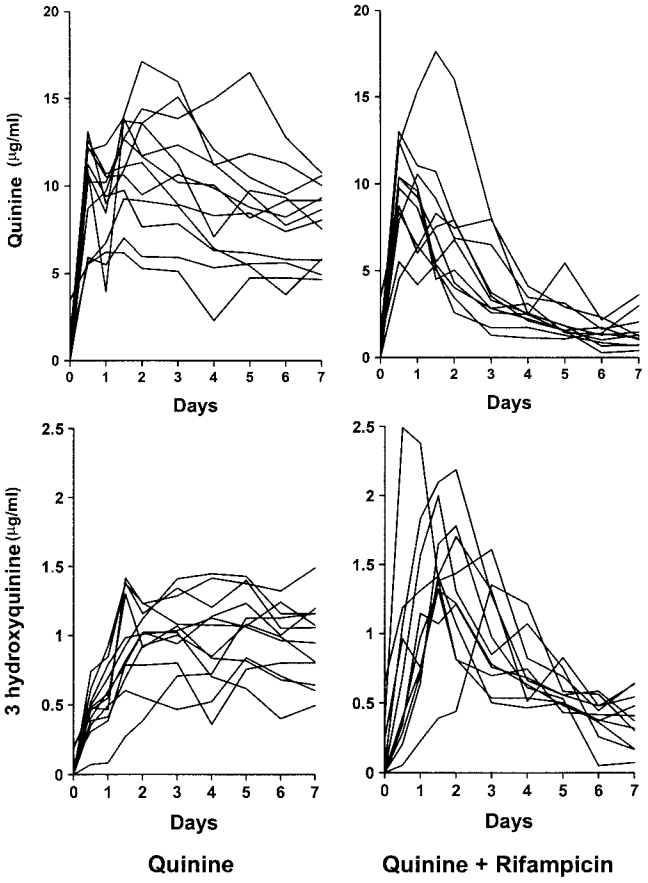

FIG. 2. Concentrations of Q and 3-OH-Q in the plasma of patients with *P. falciparum* malaria treated with Q or QR. Each line represents serial drug concentration measurements of an individual patient.

appearance of vivax or falciparum malaria. Of these 48 patients (Q = 25; QR = 23), 18 (37.5%) had a subsequent reappearance of *P. falciparum* malaria and another 9 (18.8%) had delayed appearance of vivax malaria. The recrudescence rates of falciparum malaria were five times higher (95% confidence interval, 1.8 to 16.4) in patients treated with QR (n = 15 of 23; 65%) than in those treated with Q alone (n = 3 of 25; 12%; $P < 0.001$) (Fig. 1). The time to the onset of recrudescence ranged from 13 to 23 days (mean ± SD = 17.6 ± 3.0 days) and was not significantly different between the two groups (mean ± SD = 19.0 ± 2.0 days for Q and 17.3 ± 3.1 days for QR; P = 0.37). Between patients with (n = 18) and without (n = 30) recrudescence, there were no significant differences in admission parasite counts (geometric mean = 10,605 versus 25,755; P = 0.45) or fever or parasite clearance times (median FCT_B, 49 versus 52 h [P = 0.75]; PCT, 79.4 ± 23.6 versus 73.5 ± 19.4 h [P = 0.35]).

Cryptic infection with vivax malaria occurred in nine (19%) patients. The rates of mixed malaria infection were not significantly different between the two groups (Q = 6 of 25, QR = 3 of 23; P = 1.0). The overall mean (SD) time required for vivax appearance was 20.6 (4.2) days and ranged 14 to 26 days after the start of treatment. There was no significant difference in the time to vivax appearance (within the 28-day follow-up period) between the two regimens (Q = 22.2 ± 3.7 days and QR = 17.3 ± 3.5 days; P = 0.10). One patient in the QR group had late appearance of both *P. vivax* (on day 16) and *P. falciparum* (on day 20).

Following treatment, all of the 11 patients with jaundice had normal bilirubin levels after 7 (n = 8) or 14 (n = 3) days. None of the study patients developed allergic rashes or other serious adverse effects, as monitored by clinical symptoms and laboratory data (data not shown). All patients with recurrent *P. falciparum* or *P. vivax* infections responded well to the standard treatments.

Q pharmacokinetics. Serial Q concentrations in plasma were assessed in 23 of the patients (Q alone, n = 12; QR, n = 11). On admission, none of the patients had detectable levels of Q or 3-OH-Q in their plasma, confirming that none had received Q before the study. The serial concentrations of both Q and 3-OH-Q were markedly different between the two groups (Fig. 2). Patients who received rifampin had significantly higher concentrations of 3-OH-Q initially but lower concentrations of both Q and 3-OH-Q after the second day of treatment. Indeed, whereas Q levels plateaued in the Q-alone group, they continued to decline in the QR group (Fig. 2).

The median times to C_{max} of Q and 3-OH-Q were significantly shorter in the QR group than in the Q-alone group (median = 0.5 versus 1.5 days for Q and 2 versus 4.5 days for 3-OH-Q). The overall C_{max}s of Q were approximately 10-fold higher than those of 3-OH-Q (medians, 11.24 and 1.35 μg/ml). Between the two treatment groups, the C_{max}s of Q were not significantly different (QR = 10.4 μg/ml and Q = 12.7 μg/ml; P = 0.15) but the C_{max}s of 3-OH-Q were significantly higher in patients treated with QR (1.61 versus 1.2 μg/ml; P = 0.004).

The AUC_{0-7}s of Q and 3-OH-Q were 38.6 and 5.8 μg/ml/day, respectively. The median AUC_{0-7} of Q was significantly lower in patients treated with QR than in those given Q monotherapy, and this was attributable to significantly lower Q levels between the third and seventh days of treatment (median AUC_{3-7} = 11.7 versus 47.5 μg/ml/day; $P < 0.004$). Patients treated with QR had a significantly higher level of 3-OH-Q in the first 2 days of the treatment course (AUC_{0-2}) than did those in the Q-alone group, but as Q levels fell, AUCs of 3-OH-Q followed and were significantly lower from day 3 to

day 7. The overall AUCs of 3-OH-Q in the two treatment groups were therefore not significantly different. Patients who received rifampin had significantly lower ratios of the AUC of Q to the AUC of 3-OH-Q throughout the 7-day course of therapy ($P < 0.009$), indicating higher rates of metabolic conversion of the parent compound to the metabolite. There was a significant correlation between the AUC_{0-7} of Q and the ratio of the overall AUC of Q to that of 3-OH-Q (i.e., AUC_{0-7} of Q/AUC_{0-7} of 3-OH-Q) ($r = 0.89$, $P < 0.001$).

DISCUSSION

Development of low-grade drug resistance in malaria parasites results in delays in the immediate therapeutic response and increasing recrudescence rates. The efficacy of the major antimalarial drugs has declined in recent years, and in Southeast Asia, malaria parasites have developed resistance to chloroquine, pyrimethamine-sulfadoxine, and mefloquine (21). In Thailand, there has been a slow decline in susceptibility to Q since the 1970s although monotherapy with Q given for 7 days is still 87% effective (11). In severe malaria, the decline in Q efficacy has been reflected in increasing numbers of patients with delayed parasite clearance times, but there is no convincing evidence of a change in mortality (14). In the last 2 decades, there has been greater use of Q and increasing interest in the use of antimalarial combinations to combat the emergence of resistance in falciparum malaria (10). Q has been combined with tetracycline or clindamycin, and these regimens still give 95 to 100% cure rates for falciparum malaria.

Rifampin has been shown to have antimalarial activity both in vitro against *P. falciparum* (16) and in vivo in murine malaria (1, 16). The drug has also been shown to have antimalarial activity against vivax malaria in humans (12). In plasmodia, there are two organellar DNAs that might be acted upon by polymerase targets of rifampin, those in the mitochondrion and those in the apicoplast (6). Plasmodium parasites contain an organellar circular DNA molecule that encodes the beta subunit of a prokaryocyte-like RNA polymerase (4). Rifampin is also a potent inducer of the mammalian hepatic microsomal P450 enzyme family. This may have therapeutic consequences, such as reduced oral contraceptive efficacy because of rifampin-induced estrogen metabolism. Rifampin has been shown to increase the clearance of orally administered quinidine, the D-diastereomer of Q, ninefold (3). Rifampin also increases the clearance of the structurally related quinoline methanol antimalarial mefloquine (15). The initial step in Q metabolism, like that of quinidine, is biotransformation to 3-OH-Q. This step is mediated primarily by CYP3A4 (3, 23). The hydroxy metabolite has approximately 1/10 of the antimalarial activity of the parent compound (9). A study with healthy volunteers has shown that rifampin markedly increases Q clearance (19). Acute malaria has the opposite effect, with a significant disease-induced reduction in Q clearance compared to that which occurs during convalescence (13). This results mainly from a malaria-induced reduction in hepatic mixed-function oxidase activity (principally CYP3A4). The other enzyme subfamilies that may be involved in Q metabolism are CYP1A2 and CYP2A19, but their significance in vivo has not been confirmed (7).

In the present study, which was conducted with patients with uncomplicated falciparum malaria, parasite clearance times were shorter in the QR group than in the group given Q monotherapy, suggesting that the antimalarial activity of rifampin augmented that of Q initially. However, the recrudescence rates were unexpectedly high (65%) in the rifampin recipients, five times higher than those of the Q-alone group. This large difference was explained by the marked differences in the plasma profiles of total Q concentrations when rifampin was combined with Q. When Q was given alone, its concentrations in plasma peaked in the first days of treatment and then plateaued to stay within the therapeutic range throughout the 7 days of treatment. Acute malaria reduces metabolic clearance and contracts the volume of distribution. Drug concentrations in plasma are increased as a consequence. However, as Q is a basic drug and is largely bound to the acute-phase protein α1 acid glycoprotein, the free, biologically active fraction is reduced. Recovery is associated with a decline in Q concentrations in plasma. Concentrations of the main metabolite 3-OH-Q in plasma follow the profile of the parent compound (8). Q concentrations rose during the first 48 h of treatment with QR, but this was associated with greater conversion to 3-OH-Q. Recovery was associated with a sharp decline in Q levels after the second day of treatment, which continued throughout the treatment course. The cause of the decline was enhanced metabolism. The induction of CYP450 activity by rifampin overtook the initial disease-induced dysfunction in hepatic mixed-function oxidase activity that impairs the conversion and clearance of Q during acute malaria. The induction of Q metabolism by rifampin resulted in Q concentrations falling below the therapeutic level in the second half of the treatment course and, as a consequence, resulted in a significant reduction of the cure rate from 88 to 35% in the QR group. In order to provide a cure for malaria, therapeutic drug concentrations must be present in blood for at least four asexual cycles (i.e., 8 days) (20). Falciparum malaria treatment failures in children treated with Q have also been attributed to a decline in Q levels in plasma after the fourth day of treatment (2). These results indicate that rifampin should not be combined with Q. In areas where malaria is endemic, patients with tuberculosis may also acquire malaria. The doses of Q should probably be increased in any patient who is receiving rifampin as an antituberculosis drug. This study highlights the importance of antimalarial pharmacokinetics in determining the treatment response.

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